1: Life Sci. 1996;59(18):1483-97.

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Cerebrovascular transport of Alzheimer's amyloid beta and apolipoproteins J and E: possible anti-amyloidogenic role of the blood-brain barrier.

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It is uncertain whether soluble circulating amyloid beta (sA beta) is the precursor of amyloid beta (A beta) found in cerebrovascular and parenchymal amyloid lesions in Alzheimer's Disease, and if so, how the transition to the filamentous form is brought about. Several lines of evidence suggest that apolipoprotein E (apoE) and apolipoprotein J (apoJ) may be involved in the regulation of amyloidogenesis. They both bind sA beta/A beta in vivo and in vitro. It has been suggested that apoE may modulate beta-pleated conformation of A beta and therefore act as a proamyloidogenic factor. On the other hand, apoJ as a major carrier protein of sA beta in body fluids may keep the peptide in a soluble form, thus having an anti-amyloidogenic effect. Using a well established guinea-pig brain perfusion model we have studied the blood-brain barrier (BBB) processes involved in the regulation of cerebral capillary sequestration, transport and metabolism of i) sA beta 1-40 and sA beta 1-42, synthetic peptides identical to the 40 and 42 residue forms of A beta, found primarily in vascular deposits and senile plaques, respectively; and ii) apoJ, apoE3 and apoE4 alone, and in a complex with sA beta. Specific saturable BBB luminal binding of both peptides was followed by transport into brain parenchyma and metabolism at the abluminal side of the BBB and/or in brain. The capillary sequestration of sA beta 1-40 was significant, while retention by the microvasculature of sA beta 1-42 was negligible. Binding to microvessels and blood-to-brain transport of both intact apoJ and sA beta 1-40 apoJ complexes were among the highest ever recorded for peptides and proteins at the BBB in vivo. These processes appear to be mediated by glycoprotein 330 (gp330/megalin), a receptor for multiple ligands, including apoJ. In contrast, capillary retention and transport of apoE3, apoE4 and sA beta 1-40-apoE3 complex were low to negligible, while blood-brain transport of sA beta 1-40-apoE4 was moderate. It is suggested that normal BBB may have predominantly anti-amyloidogenic functions by i) degrading sA beta during blood-to-brain transport; ii) favoring sequestration and transport of apoJ alone and in complex with sA beta via gp330 receptor-mediated mechanism and iii) excluding apoE3 and apoE4 isoforms from brain.

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